ABSTRACT

The following protocol represents a treatment approach to otherwise incurable malignant human brain tumors that is based on an antisense gene therapy strategy. This antisense strategy has been used to cause complete regression of malignant gliomas in rat brain. We and others have shown that the C6 glioma cell line produces an overabundance of insulin-like growth factor (IGF-I). We designed an episome based vector to produce multiple copies of itself when inside of the cell, and to express RNA that is anti-sense to IGF-I. Using this vector, we have demonstrated a complete suppression of IGF-I synthesis in transfected C6 glioma cells. Injection of the transfected cells subcutaneously into rats bearing C6 glioma tumors results in complete regression of tumor. This occurs whether the tumor is within the cranium or in an extracranial site at a point distant to the site of injection of the transfected cells. We have further shown that the mechanism which results in destruction of tumor includes the promotion of a CD8 T cell-mediated immune response which is selective for the glioma cells. In mixed tumors containing both C6 glioma and neuroblastoma, the T cell driven immune response remains targeted selectively to the glioma cells. This strategy of treatment is proposed in the protocol which follows. First, we will select patients with gliomas which over-express IGF-I. Second, these patients will be treated with the anti-sense strategy using the episome based vector. Finally, in the first phase of this trial we will determine toxicity which may define the limits of use for this methodology. The second phase of this study will determine efficacy as defined by changes in survival, time to tumor progression and/or to tumor regression.

This approach to gene therapy for human brain cancer has several unique advantages. First, the episome based vector includes component parts of a virus that commonly infects humans and although capable of driving extrachromosomal episomal replication, does not reproduce active virus. Second, the large copy number of the vector within transfected cells insures the expression of antisense RNA quantities sufficient to inhibit the production of IGF-I. Third the technique will not require stereotactic injection into the site of malignancy, hence surgically invasive procedures over and above those ordinarily used to diagnose and treat such brain tumors will not be needed. Finally. the mechanism for tumor distruction includes a selectively targeted T lymphocyte mediated immune response leading to the prediction that complicating toxicity should be low.